

## Suicide, depression, and CYP2D6: How are they linked?



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### Suicide risk might be increased in depressed patients who are ultra-rapid metabolizers

Genetic variations in drug-metabolizing enzymes dramatically affect drug pharmacokinetics and can result in clinically relevant differences in drug efficacy or toxicity. Cytochrome P450 (CYP) enzymes such as CYP2D6 are involved in metabolism of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), which often are a first-line choice for patients with major depressive disorder (MDD).<sup>1,2</sup> CYP2D6 is a highly polymorphic gene with 75 allelic variants (CYP2D6\*1 to \*75) and >30 additional subvariants.<sup>3</sup> These variants are associated with phenotypes where CYP2D6 activity is increased, reduced, or lost, which can increase the risk of adverse drug reactions, decrease efficacy, and possibly influence a patient's suicide risk.

In this article, we review the pharmacogenetics of CYP2D6 and discuss a possible relationship between CYP2D6 genotype and suicidal events during antidepressant treatment for MDD.

### **CYP2D6: Many variants**

CYP450 enzymes are a group of 57 proteins, each coded by a different gene. Five subfamilies in the CYP450 family metabolize most drugs: CYP1A2, CYP3A4, CYP2C19, CYP2E1, and CYP2D6.<sup>4</sup>

Researchers discovered CYP2D6 in studies of nonpsychotropics (*Box*).<sup>5-9</sup> CYP2D6 is widely expressed in many tissues, with dominant expression in the liver. Although CYP2D6 accounts for 2% of the total CYP450 liver enzyme content, it mediates metabolism in 25% to 30% of drugs in common clinical use and has a major influence on the biotransformation of SSRIs (*Table, page 18*).<sup>10</sup>

## Discovering CYP2D6's link to drug metabolism

In the late 1970s, 2 groups of researchers noted unexpected serious adverse reactions in studies of debrisoquine,<sup>5</sup> a sympatholytic antihypertensive drug, and sparteine,<sup>6</sup> an antiarrhythmic and oxytocic alkaloid drug. They observed that 5% to 10% of patients were unable to efficiently metabolize debrisoquine and sparteine and went on to define a genetic polymorphism responsible for these metabolic differences. They also observed that metabolism of antidepressants, antipsychotics,

and beta blockers also was defective in these patients.

Further investigations established that the enzyme responsible for debrisoquine metabolism was a cytochrome P450 (CYP) enzyme that is now termed CYP2D6.<sup>7</sup> In addition to biochemical evidence, the colocalization of sparteine oxidation deficiency and of the CYP2D6 locus at chromosome 22q13.1 confirmed CYP2D6 as the target gene of the debrisoquine/sparteine polymorphism.<sup>8,9</sup>

Approximately 100 polymorphic CYP2D6 alleles (variants) have been identified.<sup>3</sup> These alleles are active, resulting in normal CYP2D6 enzyme activity, or inactive, leading to decreased enzyme activity. Genotyping for most common CYP2D6 alleles in ethnically defined populations can predict poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs) with high accuracy.<sup>11</sup> PMs are compound heterozygous for inactivating alleles or homozygous for an inactivating variant. IMs carry one functional allele and one nonfunctional allele but may demonstrate a range of enzyme activity levels. EMs have 2 functional gene copies and UMs have >2 functional genes from gene duplication, resulting in ultra-rapid metabolism.

### Suicide and CYP2D6 status

The widespread use of antidepressants appears to have led to significant decline in suicide rates in many countries.<sup>12</sup> Based on an investigation of suicide mortality in 27 countries from 1980 to 2000, Ludwig and Marcotte<sup>12</sup> found that faster growth in SSRI sales per capita was associated with larger declines in suicide rates. This finding was not confounded by other suicide risk factors such as unemployment, sex, age, or divorce rate.<sup>12</sup> Countries such as Germany, Austria, Estonia, Switzerland, Sweden, Denmark, Hungary, and Slovenia—which had the highest suicide rate in the world 20 years ago (20 to 46 per 100,000 per

year)—have had impressive declines in suicide rates (24% to 57% in the last 2 decades) with a marked (6- to 8-fold) increase in SSRI prescriptions during the same period.<sup>13-15</sup> On the other hand, a few countries, such as Portugal and Spain, have experienced dramatic increases (58% and 86%, respectively) in the suicide rate with a similar increase in SSRI prescribing during the same 20-year period.<sup>16</sup>

A review of the distribution of CYP2D6 genotype among countries indicates a south/north gradient of CYP2D6 gene duplications, which indicate UM status.<sup>16</sup> The proportion of UMs increases by almost 2-fold in southern European countries (8.4% and 7% to 10% for Portugal and Spain, respectively) compared with northern European countries (1% to 2% and 3.6% for Sweden and Germany, respectively); this south/north trend extends to Africa.<sup>17</sup> The prevalence of CYP2D6 UMs is lower in northern countries, where increased antidepressant use appears to have reduced suicide rates, and higher in southern countries, where suicide rates increased despite higher antidepressant use.

Case reports and observational studies<sup>18-21</sup> suggest that compared with other CYP2D6 phenotypes, UMs may need to take higher doses of antidepressants to achieve therapeutic response. In a case report, Bertilsson et al<sup>18</sup> described 2 patients who were UMs and required high doses of nortriptyline and clomipramine to obtain appropriate plasma drug concentrations. Baumann et al<sup>19</sup> described a depressed patient with CYP2D6 gene duplication who

### Clinical Point

**Ultra-rapid metabolizers of CYP2D6 may need higher antidepressant doses to achieve a therapeutic response**



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## CYP2D6 and suicide

### Clinical Point

Depressed patients who are ultra-rapid CYP2D6 metabolizers may be more likely to commit suicide due to suboptimal antidepressant levels

#### Table

### CYP450 enzymes involved in biotransformation of SSRIs

SSRI	Enzymes involved in biotransformation
Citalopram	CYP2C19, CYP2D6, CYP3A4
Escitalopram	CYP2C19, CYP2D6, CYP3A4
Fluoxetine	CYP2D6, CYP2C9, CYP2C19, CYP3A4
Fluvoxamine	CYP1A2, CYP2D6
Paroxetine	CYP2D6, CYP3A4
Sertraline	CYP2C9, CYP2C19, CYP2D6, CYP3A4

CYP: cytochrome P450; SSRI: selective serotonin reuptake inhibitors  
 Source: Reference 10

required higher-than-usual doses of clomipramine. Rau et al<sup>20</sup> found a 3-fold increase in the frequency of UMs in a group of 16 depressed German patients who did not respond to SSRIs or serotonin–norepinephrine reuptake inhibitors, both of which are metabolized by CYP2D6. Kawanishi et al<sup>21</sup> found a significantly greater prevalence of UMs among 81 Nordic patients who did not respond to SSRIs compared with the general population.

Because suicidality may be caused by inadequately treated depressive illness, MDD patients who are UMs may be more likely to commit suicide because of suboptimal antidepressant levels. In a 2010 Swedish study, Zackrisson et al<sup>22</sup> found that compared with those who died of other causes, significantly more individuals who committed suicide had >2 active CYP2D6 genes. Stingl et al<sup>23</sup> found that among 285 depressed German patients, UMs had an elevated risk of having a high suicidality score compared with individuals with other genotypes, after adjusting for sex, baseline score on the Hamilton Depression Rating Scale (after excluding item 3 for suicidality), and number of previous depressive episodes. Other researchers found that patients with eating disorders who are UMs have a greater risk of suicidal behavior.<sup>24</sup> Although none of these 3 studies specified if these patients were treated with antidepressants, the as-

sociation between CYP2D6 gene duplication and suicide risk suggests CYP2D6's role in suicide risk might not be related solely to antidepressant metabolism.

### Effects on serotonin, dopamine

CYP2D6 is expressed in the brain and localized primarily in large principle cells of the hippocampus and Purkinje cells of the cerebellum, with no expression in other brain regions such as glial cells.<sup>25</sup> This heterogeneous expression among brain regions and cell types indicates that in addition to its role in metabolizing drugs, CYP2D6 might influence neurotransmitter levels. In vitro and in vivo animal studies suggest that CYP2D6 plays a role in biotransformation of serotonin and dopamine.<sup>26,27</sup>

**Serotonin** is likely to play a causal role in the pathophysiology of depression, and depressed patients have abnormalities in serotonin activity.<sup>28</sup> Serotonin is generated primarily from the transformation of tryptophan by tryptophan decarboxylase and tryptamine 5-hydroxylase.<sup>29</sup> Yu et al<sup>27</sup> found that CYP2D6 may be an additional pathway to regenerate serotonin through O-demethylation from 5-methoxytryptamine, but it is unclear what proportion of the physiologic pool of serotonin in synaptic nerve terminals is generated through the CYP2D6 pathway. However, this discovery provides a mechanistic basis of CYP2D6 involvement in the endogenous serotonin balance and by extension, in serotonergic physiology and neuropsychiatric disorders such as depression.<sup>30</sup> Because SSRIs target the serotonergic pathway, baseline levels of serotonin and all related components of this pathway—including CYP2D6—are likely to help determine a patient's response to SSRIs.

**Dopamine** also is generated from tyramine through CYP2D6,<sup>31</sup> and distribution of CYP2D6 in the brain follows that of dopamine nerve terminals.<sup>32</sup> The serotonergic system has strong anatomical and functional interaction with the dopaminergic system,<sup>33</sup> and imbalance between serotonin and dopamine activity is thought

to give rise to behavioral changes,<sup>2</sup> which play an important role in the development of anxiety and impulsivity.

### CYP2D6 in clinical practice

Although research into a possible link between CYP2D6 status and suicide risk in depressed patients treated with antidepressants is ongoing, at present this connection is speculative. More studies are warranted to reveal the exact role of CYP2D6 in response to SSRI treatment and suicide risk.

Knowledge of this potential association can help clinicians keep CYP450 genotyping in mind when prescribing antidepressants to depressed patients. The FDA has approved a pharmacogenetic test to analyze polymorphisms of CYP2D6 and CYP2C19.<sup>34</sup> The results of such testing might guide pharmacotherapy for depressed patients, including medication selection and dosing. For example, a patient who is a PM might be started at a lower antidepressant dosage to avoid potential adverse drug effects, whereas it might be appropriate to prescribe a higher starting dose for a UM patient to achieve an effective drug concentration.

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### Related Resources

- Peñas-Lledó EM, Blasco-Fontecilla H, Dorado P, et al. CYP2D6 and the severity of suicide attempts. *Pharmacogenomics*. 2012;13(2):179-184.
- Blasco-Fontecilla H, Peñas-Lledó E, Vaquero-Lorenzo C, et al. CYP2D6 polymorphism and mental and personality disorders in suicide attempters [published online February 11, 2013]. *J Pers Disord*. doi: 10.1521/pedi\_2013\_27\_080.

#### Drug Brand Names

Citalopram • Celexa	Nortriptyline • Aventyl,
Clomipramine • Anafranil	Pamelor
Escitalopram • Lexapro	Paroxetine • Paxil
Fluoxetine • Prozac	Sertraline • Zoloft
Fluvoxamine • Luvox	

#### Disclosure

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### Clinical Point

CYP2D6's role in suicide risk might not be solely related to antidepressant metabolism

## Bottom Line

Genetic variations in cytochrome P450 (CYP) 2D6 may increase how quickly a patient metabolizes antidepressants. Ultra-rapid CYP2D6 metabolizers may be at risk for adverse consequences of untreated depression, including suicide. CYP2D6 status also may impact a patient's suicide risk through mechanisms other than antidepressant metabolism.